migrating southward hundreds of km in spring to the Australian Alps, where they aestivate at altitudes over 1400 m, huddled in vast numbers in rock crevices and caves [18]. In autumn the same moths reverse course, reinvading their breeding grounds to the north. However, there is not a predictable compass direction over all of the bogong's range and not all populations migrate. Observations of moths near their summertime residence in the Australian Alps, mainly using a vertically-directed beam of light from ground level that enabled tallying flight direction up to an altitude of about 20 m, found that the bogong generally headed southward in spring and northward in autumn, evidently not influenced by local wind direction [18]. Not all bogong migrants, however, head in a favourable direction; some moths end up over the ocean, or arrive at New Zealand and other distant islands [19]. In the case of the bogong and other noctuid migrants, the direction of wind flows at heights at which moths are concentrated during migration and the heading of individual moths require further documentation if it is to be established that they use a sense of direction to chart their course. Relying on hitching a ride in seasonal wind patterns, as has long been held, remains the alternative and clearly simpler explanation.

A number of outstanding questions remain. How does the silver Y moth detect its heading while airborne? How does this system, presumably magnetically based [20], work and how is the preferred direction reversed with season? How sensitive is the optomotor response system for detecting wind-induced drift and is this moth able to gauge sideways drift when visual cues are reduced, as would be the case over open water? Are there backup or redundant navigational mechanisms, as appears common among migrating birds, and if so, do they have a hierarchal organization? Is the orientation system used by the silver Y responsible for directing the seasonal migration of other noctuids? It has been widely assumed that such migratory patterns rely simply on seasonal changes in wind patterns and not an intrinsic directional sense. One possible division of orientation mechanisms may be into those species, such as the silver-Y and bogong moths, that have a 'to and fro' migration that is directionally constant with season (these cases differ, however, in that the same individual bogong moths perform both migrations), and those, such as the African armyworm, that may simply use prevailing winds to arrive at directionally unpredictable and ephemeral habitats such as the inter-tropical convergence zone, and therefore do not require a directional sense. The navigational abilities of the silver Y moth, however, will cause us to re-examine these explanations.

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Mitosis: Cdh1 Clears the Way for Anaphase Spindle Assembly

The two co-activators of the anaphase-promoting complex/cyclosome (APC/C), Cdc20 and Cdh1, facilitate ubiquitination by the core complex, but their role in conferring substrate specificity has been contentious. A new report reveals that Cdc20-bound APC/C initiates the timely proteolysis of many Cdh1 substrates with the exception of the Aurora kinases. Failure to degrade Aurora kinases results in abnormal anaphase microtubule organisation and premature cytokinesis.

Fanni Gergely

A switch from high to low cyclin-dependent kinase (Cdk) activity is a prerequisite for major transitions in the cell cycle, including the initiation of anaphase, mitotic exit and the establishment of pre-replicative complexes following mitosis. A key regulator of these

events is the anaphase-promoting complex/cyclosome (APC/C), an E3 ubiquitin ligase that polyubiquitinates proteins and, thus, targets them for degradation by the 26S proteosome. Since APC/C targets a wide range of substrates for proteolysis during mitosis and the G1 phase of the cell cycle, the question arises of how a single enzyme could order the degradation of its substrates over a period of several hours with immense precision. An attractive model has been put forward as a potential solution to this problem in which intrinsic features of APC/C substrates determine the timing of their proteolysis [1]. The kinetics of ubiquitination by APC/C varies between substrates, suggesting that substrates differ in their processivity. Indeed, highly processive substrates have been found to become polyubiquitinated in a single binding event, whereas substrates with lower processivity require multiple rounds of binding to APC/C and, thus, take longer to degrade. This model alone could explain the sequential degradation of substrates seen in late mitosis [2].

However, APC/C activity itself is regulated on multiple levels. For full functionality, APC/C requires one of its two co-activators — the closely related Cdc20 and Cdh1 proteins — that facilitate substrate recruitment and ubiquitination by the core complex [3]. Although both Cdc20 and Cdh1 are abundant in G2, their association with APC/C is temporally controlled. Phosphorylation of Cdc20 by Cdk stimulates the binding of Cdc20 to APC/C (APC/C^{cdc20}) [4], but it prevents interactions between Cdh1 and APC/C (APC/C^{cdh1}) [5,6]. This results in the sequential activation of the two forms of APC/C, with APC/C^{cdc20} being active in early mitosis, coinciding with peak Cdk levels, and APC/C^{cdh1} becoming active during mitotic exit and G1, when Cdk levels plummet. APC/C activity is therefore regulated by a balance between its inhibitors and co-activators. Cdc20 and Cdh1 have also been suggested to confer some degree of substrate specificity to APC/C, but substrate recognition by core components appears equally important [7,8].

Now, a study by Floyd *et al.* [9], in this issue of *Current Biology*, not only challenges our current view of how Cdh1 contributes to APC/C function and mitotic progression but also provides unexpected novel insights into the role of Cdh1 in mammalian mitosis. The authors used RNA interference in synchronised human cell cultures to establish how Cdh1 loss of function affects mitotic exit. Surprisingly, they found that substrates previously considered as prime APC/C^{cdh1} targets (e.g., Polo-like kinase 1 (Plk1), Tpx2, survivin and Cdc20) are degraded with normal timing in the absence of Cdh1. Strikingly, of several substrates tested, only the two Aurora kinases, Aurora A [10] and Aurora B [11], showed impaired degradation in Cdh1-depleted cells. Stabilisation of Aurora B by Cdh1 depletion appeared less dramatic than that of Aurora A, which is probably due to the degradation of centromere-associated Aurora B by a distinct ubiquitin ligase complex, specifically, Cul3 [12]. Real-time single-cell analysis corroborated these findings, as fluorescently tagged forms of Plk1 and Cdc20 disappeared with normal kinetics during mitotic exit in Cdh1-depleted cells, whereas a tagged form of Aurora A remained stable [9]. Interestingly, proteolysis of Aurora A and Plk1 preceded the onset of Aurora B degradation in normal cells, suggesting that the degradation of Aurora A by APC/C^{cdh1} starts earlier than anticipated and, in fact, may coincide with the peak activity of APC/C^{cdc20}.

The most surprising aspect of these findings is that the majority of APC/C^{cdh1} substrates are successfully targeted for degradation in Cdh1-depleted cells. Importantly, proteolysis of these substrates is dependent on the APC/C core complex [9]. Therefore, APC/C^{cdc20} seems to be able to initiate the degradation of several APC/C^{cdh1} substrates during mitotic exit, thus arguing that Cdc20 and Cdh1 impose less stringency on substrate recognition than previously thought. This general lack of specificity, however, makes the requirement of Cdh1 for Aurora A and Aurora B degradation more intriguing. What is unique about the Aurora kinases? The WD40-repeat domains of Cdc20 and Cdh1 recognise short peptide motifs within APC/C substrates [4] of which the most common are the D- and KEN-boxes. The proteolysis of Aurora A, however, relies on an Aurora-A-specific A-box that functions together with a D-box in recognition by APC/C [13]. This unique A-box could prevent APC/C^{cdc20} from successfully targeting Aurora A. The requirements for the proteolysis of Aurora B by APC/C^{cdh1} are less well understood, but they are likely to involve a KEN-box and a motif similar to the A-box [14].

What are the consequences of inadequate Aurora degradation in Cdh1-depleted cells? The first and foremost effect appears to be abnormal anaphase spindle organisation [9]. Anaphase spindles in Cdh1-depleted cells have unusually large microtubule (MT) asters at their spindle poles (Figure 1). Moreover, both sister chromatid and spindle pole separation are accelerated in the absence of Cdh1, culminating in elongated anaphase spindles [9]. Proteolysis directed by APC/C^{cdh1} is therefore required for the reorganisation of the MT cytoskeleton between metaphase and anaphase. Floyd *et al.* [9] used a non-degradable Aurora A analogue to unequivocally show that stable Aurora A is responsible for these defects [9]. How can we link Aurora A degradation to anaphase spindle assembly? One possibility is that targeted proteolysis of Aurora A in the centrosome facilitates MT release or spindle pole disassembly. The rate of MT release increases upon anaphase onset and may serve to reduce the size of centrosomal MT asters [15]. Another possibility is that Aurora A degradation alters MT dynamics by changing the phosphorylation status of MT-binding proteins. It is remarkable that Aurora A degradation is required for anaphase spindle organisation, yet Aurora A levels remain high at the spindle poles until cytokinesis. Could this suggest that Cdh1 targets a specific subset of Aurora A molecules? Selective proteolysis of Aurora A molecules could be achieved by locally modulating the phosphorylation status of their A-box [16,17]. Access of APC/C^{cdh1} to different pools of Aurora A may also play a part in the degradation of the kinase, as APC/C localisation is regulated during mitosis [18].

APC/C^{cdh1} is also required for the correct timing of cytokinesis [9]. There is a significant reduction in the time taken between anaphase onset and cytokinesis in Cdh1-depleted cells when compared with mock depletions [9]. The unusually large astral MTs that form as a result of Aurora A stabilisation

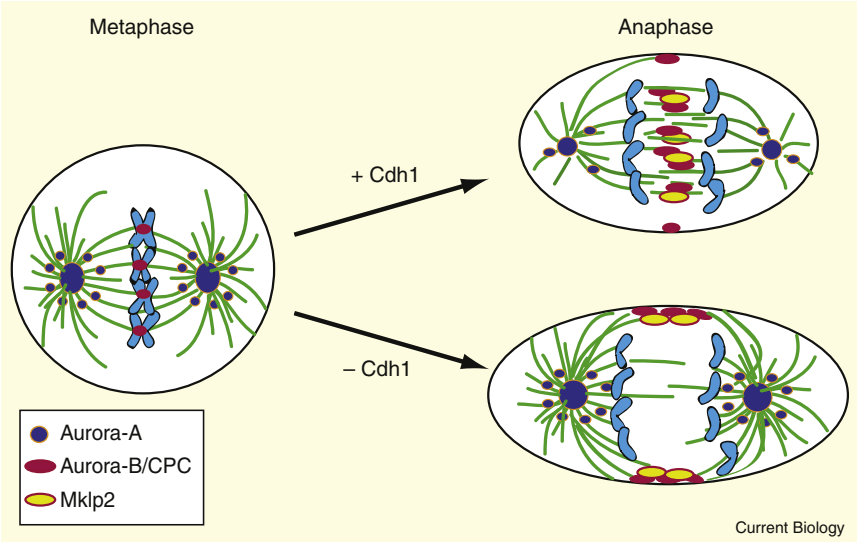

Figure 1. Schematic representation of spindle defects in Cdh1-depleted cells.

Metaphase spindle architecture is indistinguishable between mock- and Cdh1-depleted cells. Aurora A localises to the centrosome and the mitotic spindle, whereas Aurora-B/CPC is concentrated on the centromeres. In mock-depleted anaphase cells (+ Cdh1), Aurora A degradation is initiated normally. Reduction in Aurora A levels leads to the release of microtubules associated with the spindle poles and to the de-stabilisation of astral microtubules. Aurora-B–CPC–Mklp2 complexes are recruited to the midzone where they efficiently bundle microtubules and establish a robust central spindle. In Cdh1-deficient anaphase cells (−Cdh1), Aurora A is not degraded and, therefore, microtubules are neither released nor destabilised. Consequently, spindle-pole-associated asters remain large. In addition, Aurora-B–CPC–Mklp2 complexes are absent from the midzone, thus causing a weakened central spindle. Instead, Aurora-B–CPC–Mklp2 prematurely accumulates on the equatorial cortex, which may result in early onset cytokinesis.

may be sufficient to initiate cytokinesis; however, it is equally possible that the cytokinesis defect is independent of Aurora A, since Cdh1 depletion also compromises the anaphase functions of Aurora B. Aurora B is the enzymatic component of the chromosome passenger complex (CPC), which has important roles in cytokinesis. Normally, Aurora-B/CPC translocates from centromeres to the central spindle at the metaphase–anaphase transition and then onto the equatorial cortex later in anaphase. In Cdh1-depleted cells, however, Aurora-B/CPC appears sooner at the cortex. It is therefore possible that the premature cortical accumulation of Aurora-B/CPC induces the early onset of cytokinesis. Moreover, Aurora-B/CPC is absent from the spindle midzone during anaphase in Cdh1-depleted cells (Figure 1) [9]. Mklp2, the kinase responsible for targeting Aurora B to the central spindle, also fails to accumulate in the midzone [19], while the localisation of other midzone proteins (PRC1 and Mklp1) is unaffected in these cells. However, the failure to target Mklp2–Aurora-B to the midzone appears to weaken the central spindle, most likely as a result of inefficient MT bundling. Proteolysis of an unknown substrate by APC/C^{cdh1} is therefore required for the recruitment of Mklp2–Aurora-B to the spindle midzone, efficient MT bundling in the midzone, and perhaps even for the proper timing of cytokinesis.

As RNA interference can reduce but not completely eliminate protein expression, it is impossible to exclude the possibility that residual Cdh1 is sufficient to target highly processive substrates. This, in principle, could account for the differences seen between the degradation of Plk1 and Aurora A, in particular if the former is a substrate with high processivity and the latter is a substrate with low processivity. The cellular phenotype of the recently reported genetic knockout of *Cdh1* [20], however, is in good agreement with the observations described by Floyd *et al.* [9]. Similar to the effect of depleting Cdh1 by RNA interference, Cdh1-deficient mouse embryonic fibroblasts exhibit profound defects in Aurora A proteolysis and cytokinesis [20]. Genetic elimination of *Cdh1* in mice causes embryonic lethality due to placental abnormalities [20]. However, *Cdh1* knockout embryos with wild-type placentae can survive until after birth, suggesting that Cdh1 is largely dispensable for embryonic divisions. This is consistent with the idea that APC/C^{cdc20} can target several APC/C^{cdh1} substrates for proteolysis when Cdh1 is absent [9]. Mice heterozygous for the *Cdh1* knockout allele show a moderate increase in susceptibility to epithelial tumours [20]. The ability of Cdh1 to function as a tumour suppressor is less surprising when we consider the cellular effects of insufficient Cdh1 activity. Elevated mitotic kinase levels, abnormal anaphase spindle assembly and premature cytokinesis could represent a potent combination to generate aneuploidy and, therefore, increase the long-term risk of tumourigenesis.

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Evolutionary Biology: Microsporidia Sex — A Missing Link to Fungi

The evolutionary origins of the microsporidia, a group of intracellular eukaryotic pathogens, have been unclear. Genome analysis of a sex locus and other gene clusters has now revealed conserved synteny with zygomycete fungi, indicating that microsporidia are true fungi descended from a zygomycete ancestor.

Paul S. Dyer

The microsporidia are an enigmatic group of organisms. Around 1,200 species are known, all of which are obligate, intracellular pathogens [1]. They infect a wide range of species from protozoa to invertebrate and vertebrate hosts. They are eukaryotic in nature, but have a number of unusual features, such as the lack of typical mitochondria, very compact genomes and the presence of a unique coiled organelle known as the 'polar tube' or 'polar filament' (Figure 1) [1–3]. The relatively small size of certain genes combined with rapid divergence and gene loss has hindered phylogenetic analysis. Consequently, the evolutionary origins and relatedness of the microsporidia to other eukaryotic groups has been difficult to resolve. As they report in this issue of *Current Biology*, Lee *et al.* [4] instead used a novel approach, based on analysis of genome structure, to investigate genetic relatedness: their results have revealed conservation of gene synteny with zygomycete fungi at an ancestral sex locus and over 30 other gene clusters, thereby providing significant insights into the placement of the microsporidia within the fungal kingdom and the broader evolutionary biology of these pathogens.

The microsporidia have been considered as ancient 'primordial' eukaryotes because of features such as the apparent absence of mitochondria, a reduced metabolic capacity, and relatively simple cellular organization [1]. Indeed, many texts and websites still refer to the microsporidia as primitive protozoa. Recent investigations, however, have found that all is not quite what it seems. Such research has been prompted in part by the growing medical importance of the microsporidia. The incidence of infections has risen considerably since the mid-1970s as a result of a rise in number of susceptible patients, with the emergence of AIDS and the use of immunosuppressant drugs. At least 13 species of microsporidia have been reported as human pathogens, causing a diversity of diseases affecting the digestive, urinary, respiratory and nervous systems [1].

The first key insight came from indications that mitochondria had been present in ancestors of microsporidia, with relic mitochondrial genes and remnant mitosomes being detected in extant microsporidia [2,5,6]. The second insight came from genome sequencing, which revealed surprisingly small genome sizes — most likely arising from gene loss and compaction [2,3]. Both of these observations suggested that the microsporidia were in fact descended from more complex eukaryotic ancestors. A third insight came from phylogenetic analysis of an increased number of genes, which indicated that microsporidia are closely allied with the fungal kingdom, either as one of the earliest diverging

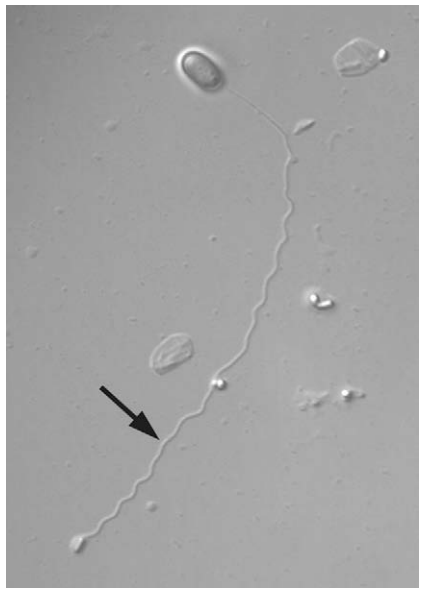

Figure 1. Spore and polar tube of *Antonospora locustae.*

DIC micrograph showing ejected polar tube (arrowed) and trailing spore (top left). The polar tube is discharged very rapidly and can pierce the membrane of potential host cells, thereby enabling infection [1]. (Photo courtesy of Patrick Keeling, University of British Columbia.)